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CENTRE INTERDISCIPLINAIRE DE RECHERCHE EN BIOLOGIE (CIRB)

CONTRÔLE MOLÉCULAIRE DU DÉVELOPPEMENT NEURO-VASCULAIRE / *MOLECULAR CONTROL OF NEURO-VASCULAR DEVELOPMENT*

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RECHERCHE

Pages web : https://www.college-de-france.fr/site/en-cirb/brunet.htm.

Neuronal and vascular development require a refined spatio-temporal orchestration to guide axons and vascular plexus through the organism, align vessels with nerves, and allow appropriate functional connections to establish between the two systems. Indeed, accurate neuro-vascular crosstalk is of tremendous importance as it regulates many vital aspects of body homeostasis such as neuronal activity and plasticity, blood pressure and heart rate.

In order to elucidate the functional aspects of neurovascular interactions, we are focusing on arterial innervation. Previous studies have established that arteries guide axons of the sympathetic nervous system toward their targets (Mukouyama Y.S *et al.*, 2002, 2005; Glebova N.O. and Ginty D.D., 2005; Makita T. *et al.*, 2008). Nevertheless, arteries themselves are also target for sympathetic innervation to exert a control of arterial blood pressure. Indeed, innervation of peripheral resistance arteries by autonomic sympathetic nerves controls response to stress and blood supply to organs by regulating vascular tone (Storkebaum E. *et al.*, 2011). This feature turns out to be critical for the regulation of homeostasis. In addition, resistance arteries bridge major elastic arteries of the arterial tree to the capillary network that perfuse all organs and tissues to provide oxygen and nutrients locally. A failure in properly regulating the caliber and vasoconstriction of resistance arteries could have devastating consequences on this vascular bed as an inappropriately high blood flow would then arise into capillaries and result in its destruction and bleeding. This vasoconstriction is the result at the cellular level of arterial smooth muscle cells (SMCs) contraction upon Noradrenalin release at the neuro-vascular junction (NVJ) site, wich is a synapse « en passant » between sympathetic axon and SMCs (Burnstock G., 2008; Luff S.E., 1996). Despite the fundamental importance of blood flow control and vascular tone, signals controlling the development of sympathetic arterial innervation remain unknown.

We first determined the developmental time window when arterial innervation is initiated, and found that arterial innervation begins during early postnatal development, two days after birth (P2). Comparing the transcriptomes of non-

innervated (P0) versus innervated arteries (P2), we identified 300 genes up-regulated in P2 arteries, and many encoded axon guidance factors, suggesting their possible implication in arterial innervation. We identified the axon guidance cue Netrin-1 as an essential factor required for development of arterial innervation in mice. Netrin-1 is produced by SMCs at the onset of innervation and signals via its receptor deleted in colorectal cancer (DCC) to attract sympathetic growth cones. Function-blocking approaches including cell-type specific deletion of the genes encoding *Ntn-1* in SMCs and *Dcc* in sympathetic neurons led to severe and selective reduction of sympathetic innervation and to defective vasoconstriction in resistance arteries. These findings reveal a novel role for Netrin-1 and DCC critical for the control of arterial innervation and blood flow regulation in peripheral organs (Brunet *et al.*, *JCI*, 2014; Eichmann and Brunet, *Science Translational Medecine*, 2014).

In addition, we identified two other molecules produced by arteries, Contactin-1 and Ephrin-A4, each of them controlling arterial innervation via a different mechanism, and involved in cardiovascular function regulation, suggesting that cardiovascular innervation is a finely tuned process (Simonnet and Brunet; Martin and Brunet, *in preparation*). Ephrin-A4 is a repulsive axon guidance molecule expressed by arteries to avoid inappropriate innervation via the receptor EPHA4 present in sympathetic neurons. Mice inactivated for EPHA4 selectively in sympathetic neurons exhibit hyper-innervated arteries, associated with an enhanced vasoconstriction. Contactin-1, expressed by arteries, is involved in axonal branching to generate new neuronal fibers at the onset of arterial innervation, as a loss of contactin-1 generate a decreased arterial innervation *in vivo*.

Finally, we showed that arterial sympathetic innervation occurs during arteriogenesis and arterial maturation, and this innervation is maintained during adulthood. Furthermore, sympathetic innervation is found on the entire arterial tree, including large elastic arteries such as the aorta, and cerebral arteries. Nevertheless, those arteries do not rely on sympathetic innervation to vasocontrict and regulate blood flow. This suggests that sympathetic innervation might be playing other roles in this context, such as arterial wall maturation or release of neuronal factors to the benefit of the artery. We are currently addressing those issues in adult mice models with conditional (THcreERT2) and/or transitory (DREADD) sympathetic innervation levels increased or enhanced.

PUBLICATION

SIMONNET É., MARTIN-PIRES S., PARDANAUD L., HENRION D., SILVESTRE J.S. et BRUNET I., « Ephrin-A4/EphA4 signaling in arterial innervation development and physiology », *in preparation*.